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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,465	02/27/2004	Mahendra S. Rao	2923-5456.1US	5295

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,465	RAO ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 15-45* is/are pending in the application.

4a) Of the above claim(s) *5-11,22-25 and 28-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12,15-21,26,27 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 8/17/06 was entered.

Claims 1-12 and 15-45 are pending in the present application.

Claims 5-11, 22-25, 28-44 were previously withdrawn because they are directed to non-elected inventions.

Accordingly, amended claims 1-4, 12, 15-21, 26-27 and new claim 45 are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(b) as being anticipated by Capecchi et al (US Patent 5,631,153; IDS) as evidenced by Sedivy, J.M. (Proc. Natl. Acad. Sci. USA 95:9078-9081, 1998; IDS) was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(e) as being anticipated by Economides et al. (US 2003/0003581 A1) as evidenced by Sedivy, J.M. (Proc. Natl. Acad. Sci. USA 95:9078-9081, 1998; IDS) was withdrawn in light of Applicant's amendment.

Claim Objections

Claims 1 and 45 are objected to because of the terms "cells" and "cell" are recited interchangeable. Please be consistent. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-5, 12, 15-17, 19-20, 26-27 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527). ***This is a modified rejection necessitated by Applicant's amendment.***

Capecchi et al teaches the use of positive-negative selector (PNS) vectors for modifying a target DNA sequence contained in the genome of a target cell capable of homologous recombination such as ES cells, hematopoietic, epithelial, liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells to correct a genetic defect or for the supplementation of the gene product of a defective gene through an *ex*

vivo gene therapy approach (see at least the abstract; col. 16, lines 10-65; and claim 21). In an exemplification, Capecchi et al teaches specifically the introduction of an exogenous functional factor VIII gene to the β-actin locus of endothelial cells isolated from a hemophiliac patient by electroporation of a PNS vector into said cells and detecting cells expressing the functional factor VIII (see example 4, cols. 25-26; Fig. 7C).

Capecchi et al does not specifically teach the preparation of homologous recombined glial progenitor cells, even though the reference teaches clearly to genetically modify hematopoietic, epithelial, liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells to correct a genetic defect or for the supplementation of the gene product of a defective gene through an *ex vivo* gene therapy approach.

However, at the effective filing date of the present application Rao et al already disclosed the preparation of a pure, homogenous population of mammalian central nervous system glial restricted precursor cells, and that these cells can be genetically modified by any means known in the art (e.g., lipofection, calcium phosphate transfection, electroporation, infection of viruses) for delivery of therapeutic or other compounds that include a gene encoding a growth factor such as a nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, glial-derived neurotrophic factor (see at least the abstract; col. 13, line 63 continues to line 45 of col. 14; and col. 19, lines 4-18).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the method of Capecchi et al by also genetically modifying the isolated pure, homogenous population of mammalian central nervous system glial restricted precursor cells of Rao et al. by homologous recombination for delivery a therapeutic compound that includes a gene encoding a growth factor, including the regions of homology are selected from the beta-actin locus. By selecting glial restricted precursor cells of Rao et al. for homologous recombination or selecting genetically modified glial restricted precursor cells expressing a supplemental gene product, the selected glial restricted precursor cells or genetically modified glial restricted precursor cells would also remain undifferentiated, express TERT and telomerase activity and have a capacity of self-renewal. Please also note that the culture medium in which the aforementioned genetically modified glial restricted precursor or progenitor cells are used for transplantation is considered to be a pharmaceutically acceptable carrier.

An ordinary skilled artisan would have been motivated to carry out the above modification because the genetically modified glial restricted precursor cells can be used to supply factors that promote neuronal survival and/or axonal regeneration (e.g., nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, glia-derived neurotrophic factor, and other factors known in the arts due to the ability of the glial cells and their precursors to integrate effectively within a host parenchyma as taught by Rao et al (col. 19, lines 4-18). Additionally, gene targeting through homologous recombination avoids many problems associated with a random integration of a heterologous gene into the genome of cells such as a wide variation in the level of

expression of such heterologous gene in transformed cells, disruption of endogenous genes which are necessary for the maturation, differentiation and/or viablility of the genetically modified cells as already noted by Capecchi et al (col. 2, lines 10-43). Furthermore, the beta-actin locus was and successfully selected for homologous recombination by Capecchi et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al and Rao et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicants' arguments related to the above rejection in the Amendment filed on 8/17/06 (pages 10-12) have been fully considered, but they are not found to be persuasive for the reasons discussed below.

Applicants argue basically that neither reference teaches or suggests homologous recombination in glial progenitor cells and that the use of homologous recombination in glial progenitor cells would not be obvious because for years, homologous recombination in somatic stem and progenitor cells has been impossible because of challenges with propagation, selection and vector selection. Applicants further argue that glial progenitor cells are distinct from neural stem cells and that they have a more limited self-renew potential, more limited ability to differentiate, and differ in

marker expression and growth factor requirements than stem cells. Thus, Capecchi et al's general disclosure of neural stem cells can not anticipate or render obvious the use of glial progenitor cells in the presently claimed invention. Applicants further argue that homologous recombination in glial progenitor cells was not obvious from either of the cited references because it is dependent on a later discovery that glial progenitor cells can be made to self-renew for prolonged time periods by exposure to a combination of growth factors and that glial progenitor cells do not undergo senescence as they express high levels of telomerase.

Firstly, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Secondly, Capecchi et al taught clearly the use of positive-negative selector (PNS) vectors for modifying a target DNA sequence contained in the genome of **any target cell** capable of homologous recombination, including hematopoietic, epithelial, liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells and others to correct a genetic defect or for the supplementation of the gene product of a defective gene through an *ex vivo* gene therapy approach. Allowed claims16-18, 20-25 in the issued US Patent indicated clearly that there is no enablement issue regarding to performing homologous recombination in somatic stem and progenitor cells.

Thirdly, Rao et al. also taught that the isolated glial progenitors are capable of extensive self-renewal without loss of differentiation potential (example 4) as well as culture conditions for these isolated glial progenitor cells (see at least the abstract; col. 6, lines 19-49).

Accordingly, amended claims 1-5, 12, 15-17, 19-20, 26-27 and 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527) for the reasons set forth above.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527) as applied to claims 1-5, 12, 15-17, 19-20, 26 and 45 above, and further in view of Weiss et al. (US Patent 5,750,376; IDS) for the same reasons already set forth in the Office Action mailed on 11/30/2005 (pages 9-11). ***The same rejection is restated below.***

The combined teachings of Capecchi et al and Rao et al have been discussed above. However, none of the reference teaches specifically the use of a gene encoding a platelet growth factor as a gene of interest, for example.

However, at the effective filing date of the present application Weiss et al already taught to genetically modify neural stem cells to produce or increase the production of a biologically active substance such as PDGF, FGF, NGF, BDNF, neurotrophins, EGF

that is useful in the treatment of a CNS disorder (col. 21, line 55 continues to lines 29 of col. 22).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the combined teachings of Capecchi et al and Rao et al by genetically modifying the isolated pure, homogenous population of mammalian central nervous system glial restricted precursor cells of Rao et al. though homologous recombination for delivery a therapeutic compound that includes a gene encoding a platelet derived growth factor in light of the teaching of Weiss et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Weiss et al already taught the gene encoding PDGF to be introduced into a neural stem cell is useful in the treatment of a CNS disorder.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al, Rao et al., and Weiss et al, coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicants' arguments related to the above rejection in the Amendment filed on 8/17/06 (page 12) have been fully considered, but they are not found to be persuasive.

Applicants argue basically that the Weiss et al reference fails to cure the deficiencies of Capecchi et al. in view of Rao et al. for the reasons already discussed above.

Please refer to the Examiner's rebuttal to Applicant's arguments regarding to the deficiencies of Capecchi et al. in view of Rao et al. above. The Weiss et al reference was used to supplement the combined teachings of Capecchi et al. and Rao et al. on the claimed embodiment in which a gene of interest is a gene encoding a platelet growth factor.

Amended claims 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527) as applied to claims 1-5, 12, 15-17, 19-20, 26 and 45 above, and further in view of Steeg et al. (Proc. Natl. Acad. Sci. USA 87:4680-4684, 1990). ***This is modified rejection necessitated by Applicant's amendment.***

The teachings of Capecchi et al and Rao et al. have been disclosed above. However, none of the references teaches specifically to introduce the gene of interest into the RNApol II locus, preferably the large subunit of RNA polymerase II encoding gene locus or RNA polr2a locus, through homologous recombination.

However, at the effective filing date of the present application Steeg et al already introduced successfully point mutations into the endogenous murine gene that encodes the largest subunit of RNA polymerase II with a vector construct containing regions of homology from the large subunit of RNA polymerase II locus (see at lest the abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the teachings of Capecchi et al and Rao et al. by also selecting the RNApol II locus, including the large subunit of RNA polymerase II encoding gene locus or RNA polr2a locus to introduce a gene of interest though homologous recombination in light of the teachings of Steeg et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Steel et al. has successfully demonstrated that specific point mutations can be introduced into the largest subunit of RNA polymerase II locus by gene targeting or homologous recombination.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al, Rao et al., and Steeg et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicants' arguments related to the above rejection in the Amendment filed on 8/17/06 (pages 12-13) have been fully considered, but they are not found to be persuasive.

Applicants argue basically that the Steeg et al reference fails to cure the deficiencies of Capecchi et al. in view of Rao et al. for the reasons already discussed above.

Please refer to the Examiner's rebuttal to Applicant's arguments regarding to the deficiencies of Capecchi et al. in view of Rao et al. above. The Steeg et al reference was used to supplement the combined teachings of Capecchi et al. and Rao et al. on the issue of selecting the RNApol II locus, including the large subunit of RNA polymerase II encoding gene locus or RNA polr2a locus to introduce a gene of interest though homologous recombination.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527) as applied to claims 1-5, 12, 15-17, 19-20, 26 and 45 above, and further in view of Economides et al. (US 2003/0003581 A1). ***This is a new ground of rejection necessitated by Applicant's amendment.***

The teachings of Capecchi et al and Rao et al. have been disclosed above. However, none of the references teaches specifically to introduce the gene of interest into the Rosa locus through homologous recombination.

However, at the effective filing date of the present application Economides et al already taught a method of targeting a promoter-less selection cassette containing a gene of interest into transcriptionally active loci, particularly into the ROSA26 locus in eukaryotic cells, stem cells and embryonic stem cells (see at least Summary of the invention, **particularly paragraphs 27-35 on page 3**).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the teachings of Capecchi et al and Rao et al. by also selecting the ROSA26 locus to introduce a gene of interest though homologous recombination in light of the teachings of Economides et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Economides et al. has successfully demonstrated that a gene of interest can be introduced into a transcriptionally active loci, particularly into the ROSA26 locus in eukaryotic cells, stem cells and embryonic stem cells by gene targeting or homologous recombination.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al, Rao et al., and Economides et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527) as applied to claims 1-5, 12, 15-17, 19-20, 26 and 45 above, and further in view of Smith et al. (US Patent 6,146,888). ***This is a new ground rejection necessitated by Applicant's amendment.***

The teachings of Capecchi et al and Rao et al. have been disclosed above. However, none of the references teaches specifically to further introduce a vector further comprising an IRES site for insertion into the glial progenitor cells.

However, at the effective filing date of the present application Smith et al already taught a method of targeting a promoter-less selection cassette containing an antibiotic resistance gene (e.g., LacZNeo) with an IRES site into mammalian stem cells (e.g., unipotential and pluripotential stem cells, somatic stem/progenitors, haematopoietic stem cells, epidermal stem cells and neuronal stem cells) for preferential expression of the antibiotic resistance gene in the stem cells that results in the preferential survival and selection of the stem cells in the presence of antibiotic (see at least the abstract; Figure 3; col. 7, lines 4-17).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the teachings of Capecchi et al and Rao et al. by further introducing a vector containing an antibiotic resistance gene with an IRES site taught by Smith et al. to select for homologous recombined glial progenitor cells that still remain undifferentiated in light of the teachings of Smith et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Smith et al already taught the introduction of a vector containing an antibiotic resistance gene with an IRES site into mammalian stem cells for preferential expression of the antibiotic resistance gene in the stem cells that results in the preferential survival and selection of the stem cells in the presence of antibiotic.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al, Rao et al., and Smith et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 12, 15-16, 19-20, 26-27 and 45 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-18, 20 and 25 of U.S. Patent No. 5,631,153 (IDS) or claims 1 of US Patent No. 6,204,061 (IDS) or claims 1-5, 7,10, 12-16 of US Patent No. 6,689,610 in view of Rao et al. (US Patent 6,235,527). ***This is a new ground of rejection.***

The instant claims are directed to a method of obtaining homologous recombination in glial progenitor cells having the steps recited in independent claims 1 and 45.

Claims 16-18, 20 and 25 of U.S. Patent No. 5,631,153 are drawn to a method for selecting a transformed cell containing a modification in a target DNA sequence in the genome of said cell having the steps recited in claim 16.

Claim 1 of U.S. Patent No. 6,204,061 is directed to a method of culturing a cell, comprising culturing a cell having a genome comprising a modification of a target DNA sequence in the genome of the cell having the steps recited in claim 1.

Claims 1-5, 7,10, 12-16 of US Patent No. 6,689,610 are drawn to a method for selecting a transformed cell containing a modification in a target DNA sequence in the genome of the cell having the steps recited in claim 1.

The claims of the present application differ from the claims of the U.S. Patent Nos. 5,631,153, 6,204,061 and 6,689,610 in reciting specifically "glial progenitor cells" and with dependent claims 26-27 further reciting the nucleic acid encoding a gene of

interest is at least a growth factor such as brain derived neurotrophic growth factor, glial derived neurotrophic factor, ciliary neurotrophic factor.

At the effective filing date of the present application, Rao et al already disclosed the preparation of a pure, homogenous population of mammalian central nervous system glial restricted precursor cells, and that these cells can be genetically modified by any means known in the art (e.g., lipofection, calcium phosphate transfection, electroporation, infection of viruses) for delivery of therapeutic or other compounds that include a gene encoding a growth factor such as a nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, glial-derived neurotrophic factor (see at least the abstract; col. 13, line 63 continues to line 45 of col. 14; and col. 19, lines 4-18).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the method in any one of the US Patent Nos. 5,631,153, 6,204,061 and 6,689,610 by also genetically modifying the isolated pure, homogenous population of mammalian central nervous system glial restricted precursor cells of Rao et al. by homologous recombination for delivery a therapeutic compound that includes a gene encoding a growth factor. By selecting glial restricted precursor cells of Rao et al. for homologous recombination or selecting genetically modified glial restricted precursor cells expressing a supplemental gene product, the selected glial restricted precursor cells or genetically modified glial restricted precursor cells would also remain undifferentiated, express TERT and telomerase activity and have a capacity of self-renewal. Please also note that the culture medium in which the aforementioned

genetically modified glial restricted precursor or progenitor cells are used for transplantation is considered to be a pharmaceutically acceptable carrier.

An ordinary skilled artisan would have been motivated to carry out the above modification because the genetically modified glial restricted precursor cells can be used to supply factors that promote neuronal survival and/or axonal regeneration (e.g., nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, glia-derived neurotrophic factor, and other factors known in the arts due to the ability of the glial cells and their precursors to integrate effectively within a host parenchyma as taught by Rao et al (col. 19, lines 4-18). Additionally, gene targeting through homologous recombination avoids many problems associated with a random integration of a heterologous gene into the genome of cells such as a wide variation in the level of expression of such heterologous gene in transformed cells, disruption of endogenous genes which are necessary for the maturation, differentiation and/or viablility of the genetically modified cells as already taught by Capecchi et al in any one of the aforementioned US Patents. Furthermore, Capecchi et al. clearly taught that any cell can be transformed with a positive-negative selection vector that is integrated into a target DNA sequence in the genome of the cell, including hematopoietic, epithelial, liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells (claim 21 of U.S. Patent No. 5,631; claim 2 of U.S. Patent No. 6,204,061; claim 6 of U.S. Patent No. 6,689,610).

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of any one of the

aforementioned issued U.S. Patents and Rao et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D.
PATENT EXAMINER